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Selenium Deficiency in Lymphedema and Lipedema—A Retrospective Cross-Sectional Study from a Specialized Clinic

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Abstract

Background: Selenium is a trace element, which is utilized by the human body in selenoproteins. Their main function is to reduce oxidative stress, which plays an important role in lymphedema and lipedema. In addition, selenium deficiency is associated with an impaired immune function. The aim of this study was to determine the prevalence of selenium deficiency in these conditions, and if it is associated with disease severity and an associated medical condition such as obesity. Methods: This cross-sectional study is an anonymized, retrospective analysis of clinical data that was routinely recorded in a clinic specialized in lymphology. The data was comprised from 791 patients during 2012–2019, in which the selenium status was determined as part of their treatment. Results: Selenium deficiency proved common in patients with lymphedema, lipedema, and lipo-lymphedema affecting 47.5% of the study population. Selenium levels were significantly lower in patients with obesity-related lymphedema compared to patients with cancer-related lymphedema (96.6 ± 18.0 µg/L vs. 105.1 ± 20.2 µg/L; $p < 0.0001$). Obesity was a risk factor for selenium deficiency in lymphedema (OR 2.19; 95% CI 1.49 to 3.21), but not in lipedema. Conclusions: In countries with low selenium supply, selenium deficiency is common, especially in lymphedema patients. Therefore, it would be sensible to check the selenium status in lymphedema patients, especially those with obesity, as the infection risk of lymphedema is already increased.

Keywords: selenium, lymphedema, lipedema, obesity, oxidative stress, inflammation

1. Introduction

Clinics specialized in lymphological diseases manage not only patients with cancer treatment-related secondary lymphedema, but also treat patients with primary lymphedema, as well as secondary lymphedema due to obesity, lipedema, or lipo-lymphedema. The pathogenesis of lymphedema is a progressive process, consisting of lymphatic leakage and stagnation, chronic inflammation, adipose tissue expansion and fibrosis [1]. In contrast to lymphedema, lipedema is characterized by bilaterally increased circumference of extremities, pain sensation, and bruising [2]. Lipedema leaves most distal parts of the body, i.e., hands and feet, unaffected. In early stages, lipedema shows increased lymphatic flow, not lymphatic insufficiency [3]. The tissue water content in lipedema patients is in the range of healthy con-

trols [4]. However, patients with lipedema may develop secondary lymphedema, if the fatty deposits compromise the lymphatic system [5]. The combination of lipedema and lymphatic impairment is called lipo-lymphedema [6].

Secondary lymphedema is mostly associated with cancer treatment as common and debilitating progressive sequelae. Recently, another reason has come to the fore: obesity-related lymphatic impairment [7]. Obesity is usually defined as a body mass index (BMI) ≥ 30 kg/m^2. In lipedema, obesity is proving to be the most common comorbidity. Up to 80% of lipedema patients are obese [8]. Obese patients with lipedema are at risk for obesity-associated lymphedema [2].

Obesity appears to be associated with selenium deficiency [9,10,11]. A reduced selenium status is significantly associated with a BMI ≥ 30 kg/m^2 in women [10,11]. Alasfar et al. showed that morbidly obese patients (BMI ≥ 40 kg/m^2) display significantly reduced serum selenium concentrations [12]. Significantly reduced selenium status in obesity appears to result from obesity-related oxidative stress [13]. Obesity is moreover associated with a state of chronic inflammation, which also contributes to the pro-oxidant environment of the condition [14].

Selenium plays an important role in inflammation and immunity [15]. Selenium deficiency negatively affects immune cells during activation, differentiation, and proliferation. This is related to increased oxidative stress. Functions like protein folding and calcium flux in immune cells may also be impaired under selenium deficient conditions [15]. Erysipelas are frequent infectious complications of lymphedema [16]. Kasseroller et al. showed that high-dose sodium selenite—an inorganic selenium form—can reduce the incidence of erysipelas [17]. Selenium status was not determined in this study or in other comparable trials [18,19,20]. Therefore, it is an open question; if selenium deficiency may be problematic, sufficiency could be protective or lymphedema treatment with high-dosed sodium selenite could be independent of selenium status.

In obesity, lymphatic function in adipose tissue and drainage capacity in the lower extremities seems to be reduced [21]. In the tissue of chronic lymphedema patients, the formation of reactive oxygen species (ROS) is enhanced and lipid peroxidation processes are accelerated [22]. Siems et al. additionally showed that reduced glutathione (GSH) concentrations in blood were decreased in chronic lymphedema patients and glutathione disulfide (oxidized glutathione; GSSG) was elevated, resulting in a three-fold higher glutathione ratio, an indicator for oxidative stress [22]. The authors concluded that the oxidative stress related changes are a consequence of the lymphedema, since the control group that had treated tumors but no lymphedema had data comparable to the healthy controls. In lipedema patients, Siems et al. showed that serum concentrations of malondialdehyde (MDA) and plasma protein carbonyls were increased compared to healthy controls [23]. Therefore, oxidative stress also plays an important role in lipedema.

The functional gene expression analysis of a mouse model of acute acquired lymphedema showed that genes involved in the immune response, stress response, and complement activation were induced in lymphedema tissue [24]. These included several, mostly stress-responsive, selenoproteins, i.e., glutathione peroxidase 1. These selenoproteins are highly dependent on an adequate selenium supply. Glutathione peroxidase 1 reaches maximal activity at plasma selenium concentrations of 95 µg/L [25]. In selenium deficiency, glutathione perox-